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Review

Optical coherence tomography of the pulmonary arteries: A systematic review

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ABSTRACT

Optical coherence tomography (OCT) is an imaging technique extensively used for visualizing the coronary circulation, where it assists clinical decision-making. Along with the new interventional procedures being introduced for pulmonary vascular disease, there is an increasing need for intravascular imaging of the pulmonary arteries. Additionally, measurements of the wall thickness of the pulmonary arteries of patients with various types of pulmonary hypertension (PH) may provide relevant diagnostic and prognostic information. The aim of this review is to summarize all the available evidence on the use of OCT for imaging the pulmonary bed and to describe a simple protocol for OCT image acquisition. We conducted a systematic review of the literature using electronic reference databases through February 2015 (MEDLINE, Cochrane Library, Web of Knowledge, and references cited in other studies) and the search terms "optical coherence tomography," "pulmonary hypertension," and "pulmonary arteries." Studies in which OCT was used to image the pulmonary vessels were considered for inclusion. We identified 14 studies reporting OCT imaging data from the pulmonary arteries. OCT was able to identify intravascular thrombi in patients with chronic thromboembolic PH (CTEPH), and an increase in vessel wall thickness was found in most patients with PH, compared with the controls. OCT has also been reported to be useful for the selection of balloon size in the setting of balloon pulmonary angioplasty for CTEPH. The main limitations include lack of standardization, little data on outcomes, cost, and the technical limitations involved in visualizing small-diameter (<1 mm) pulmonary vessels. OCT has become a potential tool for the *in vivo* study of vascular changes in the pulmonary arteries, and may provide additional information in the assessment of patients with PH. Prospective high-quality studies assessing the safety, validity, and clinical impact of OCT imaging for pulmonary vessels are warranted.

Contents

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Introduction

Pulmonary hypertension (PH) is not a disease *per se*, but a hemodynamic and pathophysiological state that can be found in multiple clinical conditions. It is defined as an increased mean pulmonary artery pressure (mPAP) of higher than 25 mmHg at rest, as assessed by right heart catheterization (RHC) [1]. The revised 2013 PH clinical classification includes five major categories with different etiological, pathophysiological, prognostic, and therapeutic features [2]. While the exact causes of PH remain under investigation, and are likely to vary with the underlying pathogenic or genetic causes, it is widely recognized that the hallmark of all forms of PH is structural alterations of the vascular wall [3].

Until recently, direct morphological assessment of the pulmonary arteries was limited to pulmonary angiography and lung biopsy [4]. Digital subtraction pulmonary angiography only images the lumen, and does not provide information on wall abnormalities; on the other hand, direct histological evaluation yields valuable information on changes in pulmonary vessel walls, but requires a thoracotomy, a potentially dangerous procedure for patients with PH [4]. Additionally, because of the difficulties in visualizing and measuring changes in the vascular walls of patients during the course of the disease, most evidence for remodeling is derived from postmortem or postoperative specimens [5].

The rapidly developing intravascular imaging modalities, intravascular ultrasound (IVUS) and optical coherence tomography (OCT), show promise for providing *in vivo* and real-time quantitative and qualitative descriptions of pulmonary vascular structures. IVUS has been validated to be a reliable method for assessing the morphology of pulmonary vessel walls, and can explore pulmonary arteries ranging from 2 to 5 mm in diameter [4,6,7]. However, the image resolution of IVUS is often insufficient for ensuring accurate assessment of changes in the walls of pulmonary arteries [8,9]. OCT is a near-infrared light source-based imaging technique with a resolution of 10–20 μm, 10-fold greater than that achieved by IVUS [10,11]. The results of several recent OCT-based studies on imaging the pulmonary arteries suggest that it is a useful tool for the *in vivo* study of the vascular remodeling process, and may have clinical impact on the diagnosis and management of PH patients. Additionally, with the development of new interventional modalities such as balloon pulmonary angioplasty (BPA) for inoperable chronic thromboembolic PH (CTEPH) [12–15] and pulmonary artery denervation for pulmonary arterial hypertension (PAH) [16], the need for intravascular imaging is increasing, and OCT may emerge as an important tool for guiding these procedures.

This review summarizes all the available data on the use of OCT for imaging the pulmonary arteries.

Methods

A systematic literature search was conducted between January 2013 and February 2015. It focused on peer-reviewed original research that investigated OCT imaging of the pulmonary arteries. The search resources included MEDLINE *via* PubMed, the Cochrane Library, Web of Knowledge, and references cited in other studies. The search employed the following terms: "optical coherence tomography," "pulmonary hypertension," and "pulmonary arteries." The search was limited to English-language articles published from January 2000 to February 2015. Studies in which OCT was used to image the pulmonary vessels and with original data were considered for inclusion. Publications that did not report original data were excluded. Conference abstracts and results posted in trial registries were excluded. No search of the gray literature was performed.

Study selection was performed by the investigators E.J. (interventional cardiologist) and R.B. (clinical cardiologist). References were managed using Mendeley Desktop software (V.1.12.3). Retrieved papers were individually searched for additional references. The citation list is available upon request. Eligible studies included participants who underwent OCT imaging of the pulmonary arteries (controls and patients with PH). The following variables were extracted, when available: year of publication, sample size, PH subgroup, diameter of imaged vessel, wall thickness, and a summary of main findings of the study.

Grading the quality of evidence of included studies

The Effective Public Health Practice Project (EPHPP) was used to rate the quality of evidence in the reviewed studies [17]. Each study was assigned a grade of strong, moderate, or weak. Studies were graded by independent reviews conducted by two of the authors (E.J., R.B.). Studies for which the two original ratings disagreed underwent a resolution review by a third author (P.M.). The results are shown in Supplementary Table 1.

Results

Study selection

Of the 29 identified publications, 15 papers were excluded because they lacked original data. Fourteen studies met the inclusion criteria and underwent quality assessment (Fig. 1). Two articles included OCT follow-up data [18,19]. The independent quality assessments were in agreement in all 14 cases (3 moderate and 11 weak). All studies were observational. The sample sizes ranged from 1 to 124 individuals. The inner diameter of the imaged pulmonary arterial vessels ranged from 0.98 mm [12] to 3.76 mm [20].

OCT technical procedures for image acquisition in the pulmonary arteries

Seven studies reported the anatomic locations of the OCT images; OCT was performed in the inferior pulmonary lobes in all

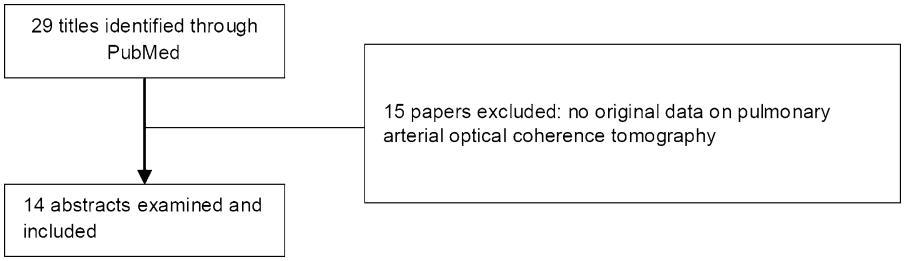

Fig. 1. Flowchart of study search and selection process.

cases [8,14,20–23]. Half of studies utilized time-domain OCT (7 studies), whereas 4 reports featured frequency-domain systems. Three studies conducted by two different investigators described similar methods for obtaining OCT images of the pulmonary arteries [12,21,23]. After gaining access to a peripheral pulmonary artery branch, they used a dedicated low-caliber occlusion balloon catheter to occlude the target vessel, in order to remove the blood and to obtain clear OCT images. Ringer's lactate solution was then infused into the artery from the distal tip of the occlusion balloon catheter at a rate of 1 to 2 mL/s. Motorized pullback OCT imaging was then performed at a rate of 1.0 mm/s for a length of 30 mm, and images were acquired at 15 frames/s [23].

OCT image interpretation and measurements

Four studies from three different groups of investigators reported the methodology used to perform measurements of the pulmonary arterial wall thickness [18,19,21,24].

Li et al. [24] conducted a necropsy-based study of 27 normal pulmonary artery segments taken from 11 patients who died of trauma. OCT was performed on segments that were subsequently processed for histological staining. The authors reported that with OCT imaging, the pulmonary arterial wall appeared as a single layer with homogeneous signal-rich bands. OCT-derived wall thickness was defined as the distance between the border of the vessel wall of the lumen to the vessel wall-lung tissue interface, and therefore encompassed the medial and intimal layers. By this criterion, the mean wall thickness of pulmonary arteries with a mean diameter of 2.1 mm was 0.162 mm. The correlation coefficient between wall thickness measured by OCT and by direct histological observation was 0.837, with a mean difference of 0.002 mm by Bland–Altman analysis, providing evidence that wall thickness measurements by OCT are accurate [24].

Domingo et al. used IVUS and OCT during a scheduled RHC to study 19 patients with PAH [21]. The authors assessed "intimal fibrosis," which was used as a surrogate for pulmonary vascular remodeling. In this model, fibrosis appeared on OCT as intimal thickening with high reflectivity, low attenuation, and a homogenous signal. The authors calculated "percentage of fibrosis" as the difference between the area limited by the outer boundary of the fibrotic area and the luminal area, divided by the luminal cross-sectional area. Interestingly, this study also found good correlation between the pulmonary arterial assessment of wall fibrosis by OCT and the histological assessments of two explanted lungs, one from a normal control participant who died of unrelated causes and one from a patient with PAH who was undergoing pulmonary transplantation.

Finally, Dai et al. used three morphometric parameters for evaluating the pulmonary arterial wall: wall thickness, thickness-diameter ratio, and wall-area ratio [19]. To calculate wall thickness, the inner border of the vessel was delineated using proprietary automated area software (St. Jude Medical, St Paul, MN, USA), and the outer border was delineated semiautomatically. A mean inner diameter and a mean outer diameter were then obtained. The difference between the inner and outer diameter was determined for the mean vessel wall thickness. The thickness-diameter ratio was defined as the wall thickness divided by the outer diameter. The wall-area ratio corresponded to the wall area (whole-vessel area subtracted from the luminal area) divided by the whole-vessel area.

OCT in pulmonary hypertension subgroups

OCT has been used for imaging of the vessel lumen and wall abnormalities in most types of PH. A summary of the studies reporting on OCT findings in the pulmonary arteries is presented in Table 1.

PAH (Group 1 PH)

Five studies included patients with PAH [9,18,19,21,25]. The feasibility of OCT imaging for a patient with PAH was first reported by Hou et al. in 2010 [9]. In this pioneer study, the authors found that the intima of the distal pulmonary artery of the PAH patient (mean cross-sectional area 1.7 mm^2) had more than twice the thickness (0.26 mm) of the intima of the normal control (0.11 mm). Subsequently, Tatebe et al. studied 17 patients with PAH and 5 control participants [25]. In this proof-of-concept study, the distal pulmonary arterial media appeared to be thickened in patients with PAH compared with the controls. Domingo et al. reported that patients with PAH with higher cross-sectional areas of fibrosis as assessed by OCT had significantly poorer hemodynamics and a worse clinical prognosis than patients with less fibrosis [21]. Dai et al. recently found that OCT can reveal the development of pulmonary arterial remodeling in patients with "borderline PH" (mPAP between 21 and 24 mmHg), and that there were significant correlations between the assessed morphometric parameters (wall-area ratio, thickness-diameter ratio, and thickness) and mPAP and pulmonary vascular resistance (PVR) [19]. The same study conducted a follow-up OCT of 14 patients with PAH who underwent treatment with pulmonary vasodilators, and demonstrated the occurrence of reverse remodeling in 8 of these patients [19]. The same group published a case report on a patient treated with sequential combination therapy consisting of beraprost and sildenafil, whom they followed by serial OCT during a three-year period. They documented a reduction in pulmonary arterial wall thickness, the thickness-diameter ratio, and wall-area ratio during treatment (Fig. 2) [18].

Pulmonary venous hypertension (Group 2 PH)

The evidence on OCT for group 2 PH, or pulmonary venous hypertension, is particularly scarce. Our group published a case report on a patient with severe mitral stenosis and associated PH who underwent balloon valvuloplasty followed by OCT of a distal segmental branch of the right pulmonary artery, which revealed diffuse thickening of the pulmonary arterial wall (Fig. 3B) [20].

Table 1
Summary of the published works on OCT imaging of the pulmonary arteries that are included in the systematic review.

First author and reference	Year	EPHPP Category	*n*	PH subgroup	OCT system	Anatomical location	Diameter of imaged vessel	Wall thickness	Main findings
Hou, J. [9]	2010	Weak	2	1 CTR 1 PAH	TD	n/a	1.75 mm 1.62 mm	0.26 mm 0.11 mm	Intima thickness twice the control
Tatebe, S. [25]	2010	Weak	32	5 CTR 17 PAH 9 CTEPH	n/a	n/a	–	–	Media is thickened in PAH vs. controls All CTEPH patients had thrombus and/or luminal flaps
Sugimura, K. [13]	2012	Weak	6	6 CTEPH	n/a	n/a	–	–	OCT is useful for evaluating the effectiveness of pulmonary angioplasty
Hong, C. [12]	2012	Weak	3	3 CTEPH	TD	n/a	0.98–3.49 mm	–	OCT visualizes peripheral small PA thrombi and differentiates red from white thrombi *in vivo*
Li, N. [24]	2012	Mod.	11	11 CTR	TD	n/a	2.14 mm	0.16 mm	Strong correlation between histology and OCT measurements of PA wall thickness. PA wall has a single-layer structure.
Hong, C. [22]	2013	Weak	1	1 CTEPH	TD	Segmental right lower lobe	–	–	OCT identified red thrombi in the peripheral PA, confirmed by histology, and it may differentiate red from white thrombi
Sugimura, K. [26]	2013	Weak	1	1 CTEPH	FD	n/a	–	–	Three-dimensional OCT demonstrates flaps and meshwork in a CTEPH patient
Tatebe, S. [8]	2013	Weak	9	9 CTEPH	n/a	n/a	–	–	OCT is apparently superior to IVUS for diagnosing CTEPH, for performing BPA and for assessing the likelihood of success of the procedure
Domingo, E. [20]	2013	Mod.	19	19 PAH	TD	n/a	–	–	The severity of OCT wall fibrosis is related to steady and pulsatile components of PA afterload and with events during follow-up
Jorge, E. [23]	2013	Weak	1	1 MS	FD	Segmental right lower lobe	3.47 mm 4.16 mm	0.28 mm 0.31 mm	OCT images showed diffuse thickening of pulmonary artery wall
Sánchez-Recalde, A. [21]	2014	Weak	1	1 CTEPH	FD	Basal segment right lower lobe	–	–	OCT showed multiples fibrous tracts forming a honeycomb-like structure, with recanalized thrombosis and intimal thickening
Roik, M. [14]	2014	Weak	1	1 CTEPH	FD	Segmental left lower lobe			OCT is useful for precisely determining the location of target lesion for BPA and for choosing the appropriate balloon size and length
Dai, Z. [18]	2014	Mod.	1	1 PAH	TD	Segmental middle and right lower lobe	3.45 mm	0.28 (before Tt) 0.17 (after Tt)	OCT is useful for documenting the regression of pulmonary arterial remodeling in response to medical treatment.
Dai, Z. [19]	2014	Weak	124	79 PH* 10 borderline PH 35 CTR	TD	n/d	–	–	The morphometric parameters analyzed by OCT (PA wall thickness, thickness-diameter ratio, and wall-area ratio) were significantly correlated with mean PAP and PVR. OCT can demonstrate the development of PA remodeling in borderline PH (mean PAP between 21 and 24 mmHg). OCT follow-up was performed in 14 PAH patients, demonstrating the occurrence of reverse remodeling in response to pulmonary vasodilatory treatment.

BPA, balloon pulmonary angioplasty; CTEPH, chronic thromboembolic pulmonary hypertension; CTR, control; EPHPP, Effective Public Health Practice Project; IVUS, intravascular ultrasound; FD, frequency domain; Mod., moderate; MS, mitral stenosis; OCT, optical coherence tomography; PA, pulmonary artery; PAH, pulmonary arterial hypertension; PAP, pulmonary artery pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; TD, time domain; Tt, treatment.
* PH subgroups not reported.

Chronic thromboembolic pulmonary hypertension (Group 4 PH)

Group 4 PH, or CTEPH, has also been a focus of OCT assessment for interventional therapy using BPA, an invasive procedure being introduced for patients with inoperable CTEPH [13]. A study that enrolled 9 patients with CTEPH found that all had pathological findings on OCT: 4 patients presented with occlusion of the pulmonary artery, probably by thrombus, whereas 6 patients had luminal flaps [25]. The same investigators reported on the usefulness of OCT for accurately measuring the pulmonary arterial luminal diameter in order to determine the size of the balloon to use for BPA. OCT was found to be more useful than IVUS, because it can also predict the failure of BPA, by showing the persistence of the occlusion of a lumen by a thrombus after inflation of the balloon [8]. Roik et al. published a clinical case that also suggested that OCT was effective at precisely locating the target lesion for BPA and for determining the appropriate balloon size and length

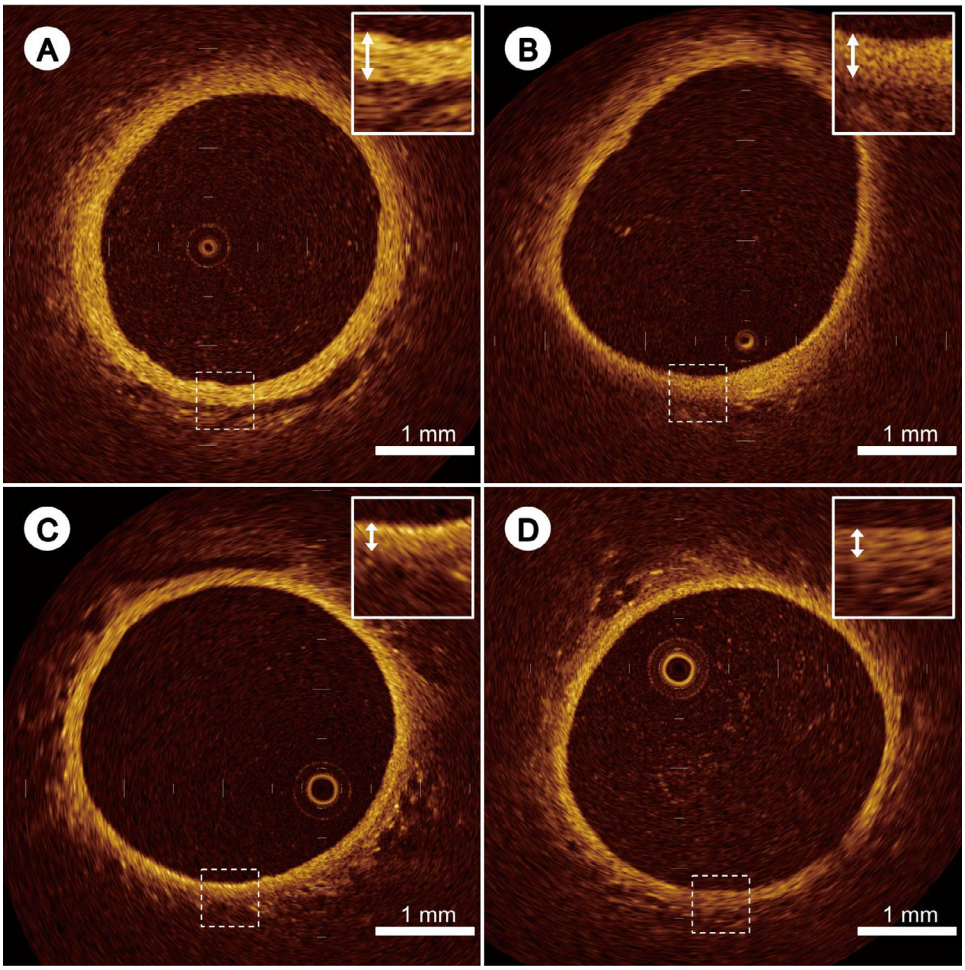

Fig. 2. Serial optical coherence tomography (OCT) of the pulmonary artery during medical treatment. (A) The first OCT examination (12 August 2009) showed remodeling of the right anterior basal segmental artery, approximately 3.5 mm in diameter, which is consistent with OCT findings of intimal fibrosis (mean outer diameter, 3.45 mm; outer area, 9.35 mm^2; wall-area ratio, 0.302; thickness-diameter ratio, 0.081; and thickness, 0.28 mm). Serial OCT showed that medical treatment induced (B) progressive improvement with pulmonary arterial remodeling on 25 November 2009 of the lateral segmental artery (mean outer diameter, 3.42 mm; outer area, 9.24 mm^2; wall-area ratio, 0.247; thickness-diameter ratio, 0.067; and thickness, 0.23 mm) in the right middle lobe, (C) complete regression on 13 August 2010 in the apical segmental artery (mean outer diameter, 3.43 mm; outer area, 9.27 mm^2; wall-area ratio, 0.202; thickness-diameter ratio, 0.052; and thickness, 0.18 mm) in the right lower lobe, and (D) sustained complete regression on 18 February 2011 in the right pulmonary artery in an undocumented specific location (mean outer diameter, 3.43 mm; outer area, 9.24 mm^2; wall-area ratio, 0.187; thickness-diameter ratio, 0.049; and thickness, 0.17 mm). (Inset) High-power image of section of pulmonary arterial wall (dashed-line box). Arrows, wall thickness.
Reproduced with permission from Dai et al. Visualization of complete regression of pulmonary arterial remodeling on optical coherence tomography in a patient with pulmonary arterial hypertension. Circ J 2014;78:2771–3.

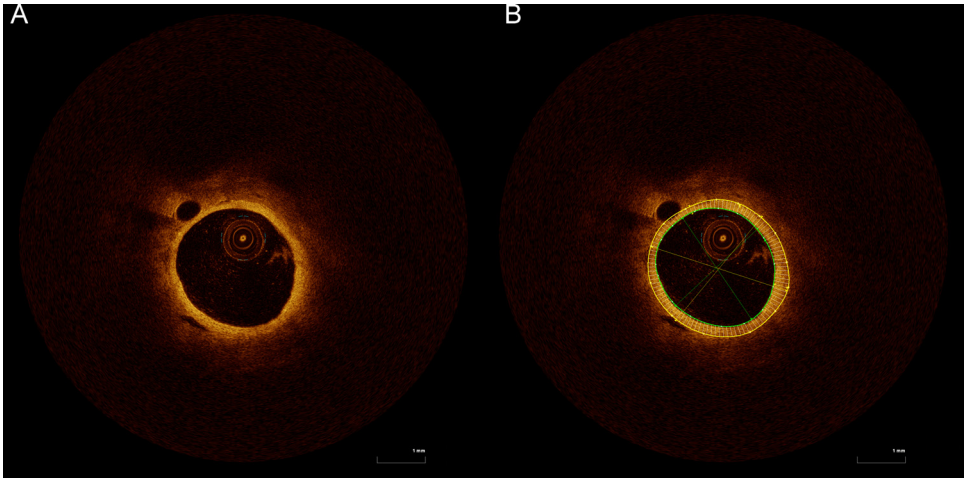

Fig. 3. Optical coherence tomography (OCT) images of a distal pulmonary artery (mean diameter of 2.45 mm) in the lower left lobe of a patient with mitral stenosis and pulmonary hypertension (mean pulmonary artery pressure 26 mmHg). (A) OCT image showing a vessel wall with a single layer. (B) To increase reproducibility, the mean vessel wall thickness can be calculated as the mean difference between the outer wall border (manually delimited) and the luminal border (automatically rendered). In this case, the mean vessel wall thickness was 0.21 mm.

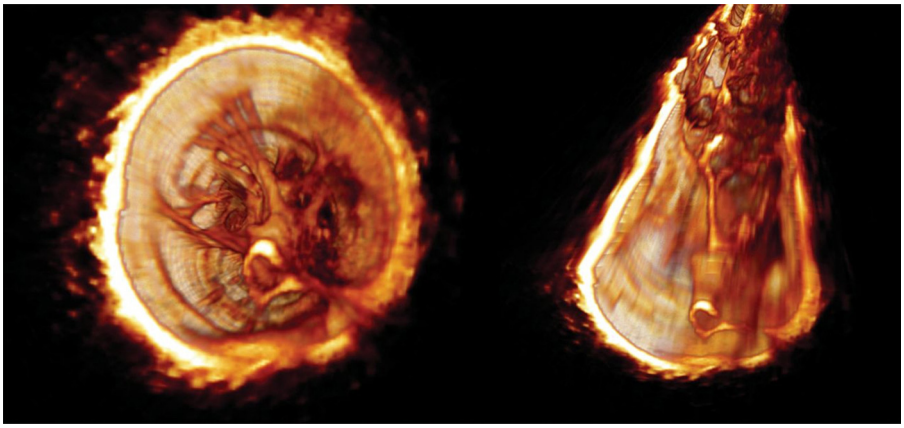

Fig. 4. Three-dimensional-optical coherence tomography (3D-OCT) imaging showed flaps and meshwork of the pulmonary arteries in a patient with chronic thromboembolic pulmonary hypertension
Reproduced with permission from Sugimura *et al.* Three-dimensional-optical coherence tomography imaging of chronic thromboembolic pulmonary hypertension. Eur Heart J 2013;34:2121.

[14]. Sugimura et al. recently presented for the first time three-dimensional OCT images of the pulmonary arteries of a CTEPH patient, clearly showing the unresolved thrombi, with the flaps and meshwork characteristic of this form of PH [26] (Fig. 4). Sánchez-Recalde published OCT images from a CTEPH patient that showed multiple fibrous tracts forming a honeycomb-like structure with recanalized thrombosis and intimal thickening [22]. The ability of OCT to differentiate red from white thrombi in the peripheral pulmonary artery *in vivo* was reported by Hong et al. in a study involving 3 patients [23]. Using OCT signal attenuation proprieties, the authors identified small peripheral thrombi missed by other imaging techniques, as only erythrocytes can scatter near-infrared light [12]. The results of the study of Tatebe et al. suggest that OCT was useful for differentiating between the precapillary PH groups, as all had similar hemodynamic characteristics, despite different pathological characteristics [25].

No complications were reported in the reports that we reviewed, which highlights the safety of OCT.

Discussion

OCT technical procedures for image acquisition in the pulmonary arteries

All 7 studies reporting the anatomic location where OCT was performed used the inferior pulmonary lobes. This location is in accordance with previous histopathological and IVUS studies that found more severe vascular abnormalities in the lower lobes than in the upper lobes [27,28]. In contrast, no differences were found between the right and left lungs in an IVUS-based study [27].

The first commercially available OCT system was the LightLab M2 time-domain TD-OCT imaging system (LightLab Imaging Inc., Westford, MA, USA), followed by the frequency-domain FD-OCT system (C7 XR, LightLab) [29]. FD-OCT systems have higher frame rates and scanning speeds, enabling acquisition of pullback images rapidly during a brief infusion of contrast. However, the diameter of the ImageWire^{TM} TD-OCT system is smaller (0.48 mm), a feature that can be advantageous when exploring small vessels.

Regarding OCT technical procedures for image acquisition, our group used a technique that does not require balloon occlusion of the target vessel, differently from the protocols used by Domingo et al. and Hong et al. In our protocol, the pulmonary artery is gently catheterized by a Swan-Ganz catheter *via* a femoral, jugular, or brachial approach. The Swan-Ganz catheter is then changed over the wire to a 6-Fr Judkins right guide catheter. A 0.0014″ standard guidewire is then positioned distally in the pulmonary vessel in the inferior pulmonary lobe, and a FD-OCT catheter (C7 Dragonfly Catheter; St. Jude Medical) is advanced (Fig. 5). In order to remove all the blood, as well as to obtain clear images, iodinated contrast is infused at a flow rate of 5 mL/s over 4 s, at 400 lb/in^2 of pressure (Medrad Mark V Provis angiographic injection system). OCT

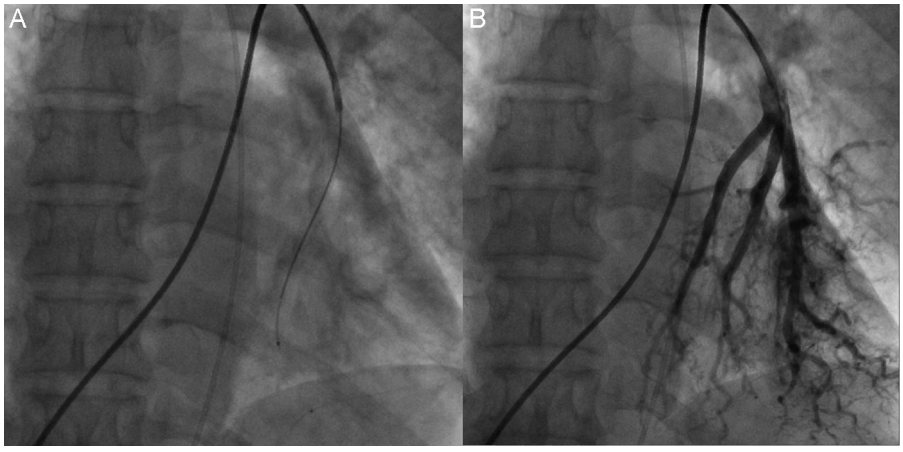

Fig. 5. (A) Optical coherence tomography probe in the same (Fig. 3) distal pulmonary artery in the lower left lobe. A 6-Fr Judkins right coronary artery guide catheter was used. (B) Pulmonary angiography of the imaged segment.

Table 2
Protocol for optical coherence tomography imaging of the pulmonary arteries.

Before imaging
Identify the patient and target vessel in the console
Flush the OCT catheter with iodinated contrast
Connect the OCT catheter to the imaging console
Connect the OCT catheter to the motorized pullback system
Activate and verify that an image is generated before insertion
During imaging
Catheterize the pulmonary artery using a right Judkins 6 French guide catheter
Position a 0.0014″ standard guidewire distally in the pulmonary artery through the guiding catheter
Advance the OCT catheter
Infuse iodinated contrast at a flow rate of 5 mL/s for 4 s, at 400 psi
Scan the vessel with the integrated automated pullback device at 20 mm/s
Acquire the OCT images
After imaging
Adjust calibration
Perform the measurements in the most distal vessels imaged in each lobe
Delineate the inner border of the vessel using the automated area software and the outer border semiautomatically to measure mean vessel wall thickness
Store the images in DICOM digital format with the same identification name of the angiographic images
Prepare a report that includes measurements and qualitative image interpretation

OCT, optical coherence tomography; DICOM, Digital Imaging and Communications in Medicine.

images are acquired using a C7-XR OCT Intravascular Imaging System (St. Jude Medical) and digitally archived. The vessel is scanned using the integrated automated pullback device at 20 mm/s. This method uses material that is easily available from any adult interventional cardiology catheterization laboratory, and does not require specific low-caliber occlusion balloon catheters (Table 2). Three-dimensional images may be obtained after postprocessing of the cross-sectional images (Fig. 6). Morphometric assessment of the vessels can be performed offline on the archived images.

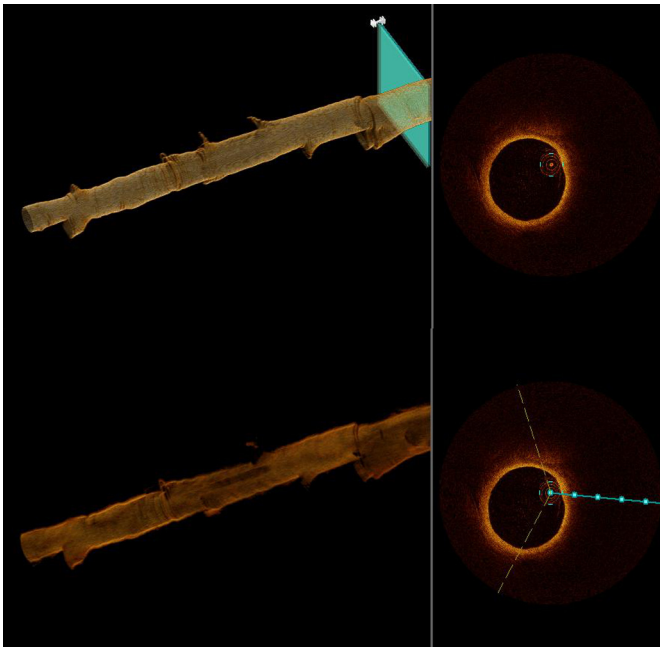

Fig. 6. Three-dimensional optical coherence tomography images taken from the same segment of the pulmonary artery (Fig. 3). Vessels sprouting from the main artery are clearly visible. Upper panel: Three-dimensional tubular reconstruction of the vessel. Lower panel: Three-dimensional view of the same vessel with the lumen exposed.

OCT image interpretation and measurements

An important feature for consideration when analyzing OCT images of the pulmonary arterial wall is that in contrast to the walls of the coronary arteries, which appear as three-layered structures, OCT images of pulmonary arteries show a single layer, with homogeneous, signal-rich bands (Fig. 3A) [24]. Therefore, OCT cannot clearly discriminate the intima from the media. One possible reason for this observation is that unlike coronary arteries, which have a media consisting of 10–20 layers of vascular smooth muscle cells, the media of normal pulmonary arteries is particularly rich in elastic fibers, which strongly reflect light, leading to a unique aspect [24]. This single-layered appearance of the pulmonary arteries on OCT may affect the different methods for assessing wall thickness, the hallmark of pulmonary vascular disease. Additionally, the clinical relevance and the prognostic impact of the concepts "medial hypertrophy" or "intimal fibrosis", which are referred to in some IVUS and OCT reports, remain controversial. In a pivotal histopathological study conducted on patient samples from the National Institutes of Health PAH registry, all patients had medial hypertrophy, with most having intimal fibrosis [30]. Delgado et al., in a study that included histopathological analysis of the pulmonary vasculature of patients dying of advanced heart failure, found that patients with a PVR greater than 2.5 Wood units had greater hypertrophy of the media, compared with patients with a PVR less than 2.5 Wood units. Neither group of patients was found to have pathologically significant intimal fibrosis in their arteries [31]. On the other hand, Palevsky et al. showed that only the area of intimal fibrosis was significantly different between patients with PH who exhibited rapid deterioration and those PH patients who remained stable on follow-up [32]. Notably, as previously stated, IVUS cannot be used for accurate measurement of wall thickness, because of the strongly echogenic pulmonary arterial wall and the difficulty in defining the adventitial border [9,33]. The use of OCT for differentiating the media from the intima may be challenging; however, its ability to identify clearly the luminal and the adventitial borders supports the argument in favor of reporting "wall thickness," instead of "intimal fibrosis" or "medial hypertrophy" [34].

Finally, because wall thickness is closely associated with vessel diameter, the thickness-diameter ratio and the wall-area ratio might be the most adequate parameters for representing vascular remodeling of the pulmonary wall and for assessing patients and controls in comparative studies and during follow-up evaluations [35].

OCT for pulmonary hypertension subgroups

It is widely recognized that structural alterations of the pulmonary vascular wall contribute to all forms of PH. Characteristic features of the remodeled vasculature include increased stiffening of the proximal elastic pulmonary arteries; thickening of the intimal and/or medial layer of muscular arteries; development of vaso-occlusive lesions; and the appearance of cells that express markers specific to smooth muscle cells in normally nonmuscular small-diameter vessels. The appearance of these cells in the walls of nonmuscular vessels is the result of the migration and proliferation of pulmonary arterial smooth muscle cells and cellular transdifferentiation [3]. The final result is that the arterial vascular wall becomes thicker and stiffer, which changes its behavior in terms of elasticity, pulsatility, and compliance [5].

Interestingly, there are also reports stating that these microstructural alterations may extend to larger pulmonary arteries [36,37]. A recent study by Lau et al. that used IVUS to assess PAH patients found that pulmonary arteries ranging from 2 to 5 mm in

diameter showed diffuse wall thickness and increased stiffness, compared with controls. These results challenge the concept that only pulmonary arterioles (with diameters ranging from 300 to 500 μm) are affected in PAH [36]. In accordance with previous histopathological and IVUS studies [4–7,27,30,32,34,36], the OCT studies of PAH patients that we analyzed also showed that the pulmonary arterial wall appeared to be thicker, compared with controls [9,19,25].

Regarding the prognostic impact of the intravascular imaging techniques, several IVUS-based studies reported that the severity of pulmonary arterial morphological changes was of no value in predicting mortality [4,6,7]. Conversely, Domingo et al. found that the severity of OCT-measured "intimal fibrosis" was significantly negatively correlated with the capacitance of pulmonary arterial vessels and was also predictive of unfavorable clinical outcomes during mid-term follow-up [21]. The same study reported a positive association between the severity of "intimal fibrosis" and the steady and pulsatile components of the right ventricular afterload [21]. In support of this finding, Dai et al. demonstrated that the pulmonary arterial wall thickness, thickness-diameter ratio, and wall-area ratio were significantly correlated with the mPAP and PVR. Importantly, this latter work also demonstrated that OCT can identify the development of pulmonary arterial remodeling during the very early stages of PH, when the mPAP is in the range of 20–24 mmHg [19]. This finding may be important for the management of "borderline PH" patients [38]. Additionally, reverse remodeling after specific vasodilator therapy was observed in a significant proportion of PAH patients enrolled in an OCT follow-up study [19]. These studies shed some light on the role of OCT for documenting the impact of pulmonary vasodilator therapy on vascular remodeling in patients with PAH.

The histopathological specimens of group 2 PH patients manifest not only the expected congestive vasculopathy, but also features compatible with pulmonary arterial disease, such as medial hypertrophy or intimal fibrosis. The classical model of this condition is mitral stenosis [39]. Bressollette et al. used IVUS to assess patients with mitral stenosis and PH, and found that they had thinner pulmonary arterial walls than patients with other PH etiologies, a finding that may be associated with a greater degree of PH reversibility after mitral valve intervention [27]. These findings support the concept that pulmonary arterial wall thickness can provide relevant prognostic information.

CTEPH: a particular indication

Eight of the fourteen analyzed publications included patients with CTEPH, which currently is the subgroup of PH patients for whom OCT imaging has demonstrated the greatest practical applicability. OCT has emerged as an important tool for guiding BPA, for both precisely localizing the target lesion and determining the correct balloon size for the procedure [13,14,25]. In theory, OCT may have the potential for improving the efficacy and safety of BPA. Additionally, OCT demonstrates pathological manifestations typical of this subgroup of PH, which are thrombi and luminal flaps [22,25,26], and therefore might play a role in the assessment of specific patients for whom other imaging modalities may miss the diagnosis [12].

Limitations of OCT

Despite the potential advantages of pulmonary arterial OCT imaging over other available techniques, there are limitations of this method that warrant mentioning. OCT is an invasive and expensive technique that prolongs RHC, and, as with any other invasive vascular technique, there are potential complications stemming from use of a wire and catheter, such as dissection or perforation. Thus far, there have not been any reported complications associated with the use of this technique in the pulmonary vessels.

OCT imaging needs a blood-free imaging field, which is achieved by transient occlusion of the proximal flow through the artery or by the injection of iodinated radiographic contrast. These procedures may result in transient tissue ischemia; although, since there is a rich oxygen supply to lung tissues, a temporary occlusion of blood flow to the distal pulmonary arteries might not lead to serious complications.

OCT has limited tissue penetration (2–3 mm) and cannot fully image large-caliber vessels. Additionally, as only case reports and small series have been published to date, OCT still has limited applicability in pulmonary vascular disease. Therefore, defining normal and pathological findings is difficult. Finally, its clinical prognostic impact is unclear, because robust outcome data are still needed. Only prospective clinicopathological studies using standardized imaging methodology can help clarify the role of OCT in the pulmonary vascular diseases.

Current clinical applications and future perspectives

With the development of new pulmonary arterial interventional modalities, the need for intravascular imaging may also increase. OCT may emerge as a tool for guiding these procedures. Currently, the predominant indications for OCT imaging of the pulmonary vessels include the assessment of patients with CTEPH for BPA and as an ancillary tool for the differential diagnosis of subgroups of PH, namely PAH from CTEPH. Also, the use of three-dimensional OCT rendering may facilitate image interpretation. New technologies may enable higher frame rates, deeper penetration, faster pullbacks, and even the acquisition of spectroscopic data [40], thereby allowing even more accurate tissue characterization.

Conclusions

OCT has arisen as a tool for the *in vivo* study of vascular changes in the pulmonary arteries and may provide additional information in the assessment of patients with PH. Currently, its main clinical use is for CTEPH-related interventions. Prospective high-quality studies are warranted to confirm the safety, validity, and clinical impact of OCT imaging applied to pulmonary vessels.

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Conflict of interest

E.J. has received research grants from St. Jude Medical. R.B., J.C., H.F., M. Pan, P.M. and M. Pêgo declare that they do not have any conflict of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jjcc.2015.09.024.

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